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PTO/SB/05 (4/98)  
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# UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 C.F.R. § 1.53(b))

Attorney Docket No. IMET0040

First Inventor or Application Identifier Hazen et al.

Title A Method of Characterizing Spectrometer Instruments and..

Express Mail Label No. EL540885975US

## APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: Assistant Commissioner for Patents  
Box Patent Application  
Washington, DC 20231

1. ☒ \* Fee Transmittal Form (e.g., PTO/SB/17)  
(Submit an original and a duplicate for fee processing)
2. ☒ Specification [Total Pages 23]  
(preferred arrangement set forth below)
- Descriptive title of the Invention
  - Cross References to Related Applications
  - Statement Regarding Fed sponsored R & D
  - Reference to Microfiche Appendix
  - Background of the Invention
  - Brief Summary of the Invention
  - Brief Description of the Drawings (if filed)
  - Detailed Description
  - Claim(s)
  - Abstract of the Disclosure
3. ☒ Drawing(s) (35 U.S.C. 113) [Total Sheets 5]
4. Oath or Declaration [Total Pages 3]
- a. ☒ Newly executed (original or copy)
  - b. ☐ Copy from a prior application (37 C.F.R. § 1.63(d))  
(for continuation/divisional with Box 16 completed)
  - i. ☐ DELETION OF INVENTOR(S)  
Signed statement attached deleting  
inventor(s) named in the prior application,  
see 37 C.F.R. §§ 1.63(d)(2) and 1.33(b).

5. ☐ Microfiche Computer Program (Appendix)
6. Nucleotide and/or Amino Acid Sequence Submission  
(if applicable, all necessary)
- a. ☐ Computer Readable Copy
  - b. ☐ Paper Copy (identical to computer copy)
  - c. ☐ Statement verifying identity of above copies

## ACCOMPANYING APPLICATION PARTS

7. ☒ Assignment Papers (cover sheet & document(s))
8. ☒ 37 C.F.R. § 3.73(b) Statement ☒ Power of  
(when there is an assignee) Attorney
9. ☐ English Translation Document (if applicable)
10. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
11. ☐ Preliminary Amendment
12. ☒ Return Receipt Postcard (MPEP 503)  
(Should be specifically itemized)
13. ☒ \* Small Entity Statement(s) ☐ Statement filed in prior application,  
(PTO/SB/09-12) Status still proper and desired
14. ☐ Certified Copy of Priority Document(s)  
(if foreign priority is claimed)
15. ☐ Other: .....

\* NOTE FOR ITEMS 1 & 13: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY  
FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT  
IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).

16. If a CONTINUING APPLICATION, check appropriate box, and supply the requisite information below and in a preliminary amendment

☐ Continuation ☐ Divisional ☒ Continuation-in-part (CIP) of prior application No. 09 / 359,191

Prior application information: Examiner Unknown

Group / Art Unit: Unknown

For CONTINUATION or DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 4b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

## 17. CORRESPONDENCE ADDRESS

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Name

Address

City

State

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Country

Telephone

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Name (Print/Type)

Michael A. Glenn

Registration No. (Attorney/Agent)

30,176

Signature

Date

9/18/2000

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## for FY 1999

Patent fees are subject to annual revision.  
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See 37 C.F.R. §§ 1.27 and 1.28.

TOTAL AMOUNT OF PAYMENT (\$ ) 439.00

## Complete if Known

Application Number	Unassigned
Filing Date	Herewith
First Named Inventor	Hazen et al.
Examiner Name	Unassigned
Group / Art Unit	Unassigned
Attorney Docket No.	IMET0040

## METHOD OF PAYMENT (check one)

1. ☐ The Commissioner is hereby authorized to charge indicated fees and credit any over payments to:

Deposit Account Number 07-1445

Deposit Account Name Michael Glenn

☒ Charge Any Additional Fee Required  
Under 37 CFR §§ 1.16 and 1.17

2. ☒ Payment Enclosed:  
☒ Check ☐ Money Order ☐ Other

## FEE CALCULATION

## 1. BASIC FILING FEE

Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description	Fee Paid
101 760	201 380	Utility filing fee	345.00
106 310	206 155	Design filing fee	
107 480	207 240	Plant filing fee	
108 760	208 380	Reissue filing fee	
114 150	214 75	Provisional filing fee	

SUBTOTAL (1) (\$ ) 345.00

## 2. EXTRA CLAIM FEES

Total Claims	Extra Claims	Fee from below	Fee Paid
26	-20** = 6	9	54.00
2	-3** = 0	39	0.00
Multiple Dependent			

\*\*or number previously paid, if greater, For Reissues, see below

Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description
103 18	203 9	Claims in excess of 20
102 78	202 39	Independent claims in excess of 3
104 260	204 130	Multiple dependent claim, if not paid
109 78	209 39	** Reissue independent claims over original patent
110 18	210 9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) (\$ ) 54.00

## FEE CALCULATION (continued)

## 3. ADDITIONAL FEES

Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description	Fee Paid
105 130	205 65	Surcharge - late filing fee or oath	
127 50	227 25	Surcharge - late provisional filing fee or cover sheet	
139 130	139 130	Non-English specification	
147 2,520	147 2,520	For filing a request for reexamination	
112 920*	112 920*	Requesting publication of SIR prior to Examiner action	
113 1,840*	113 1,840*	Requesting publication of SIR after Examiner action	
115 110	215 55	Extension for reply within first month	
116 380	216 190	Extension for reply within second month	
117 870	217 435	Extension for reply within third month	
118 1,360	218 680	Extension for reply within fourth month	
128 1,850	228 925	Extension for reply within fifth month	
119 300	219 150	Notice of Appeal	
120 300	220 150	Filing a brief in support of an appeal	
121 260	221 130	Request for oral hearing	
138 1,510	138 1,510	Petition to institute a public use proceeding	
140 110	240 55	Petition to revive - unavoidable	
141 1,210	241 605	Petition to revive - unintentional	
142 1,210	242 605	Utility issue fee (or reissue)	
143 430	243 215	Design issue fee	
144 580	244 290	Plant issue fee	
122 130	122 130	Petitions to the Commissioner	
123 50	123 50	Petitions related to provisional applications	
126 240	126 240	Submission of Information Disclosure Stmt	
581 40	581 40	Recording each patent assignment per property (times number of properties)	40.00
146 760	246 380	Filing a submission after final rejection (37 CFR § 1.129(a))	
149 760	249 380	For each additional invention to be examined (37 CFR § 1.129(b))	

Other fee (specify) \_\_\_\_\_

Other fee (specify) \_\_\_\_\_

\* Reduced by Basic Filing Fee Paid

SUBTOTAL (3) (\$ ) 40.00

## SUBMITTED BY

Name (Print/Type)	Michael Glenn	Registration No. (Attorney/Agent)	30,176	Telephone	650-474-8400
Signature		Date	9/18/2000		

Complete (if applicable)

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**STATEMENT CLAIMING SMALL ENTITY STATUS  
(37 CFR 1.9(f) & 1.27(c))--SMALL BUSINESS CONCERN**

Docket Number (Optional)  
IMET0040

Applicant, Patentee, or Identifier: Hazen et al.

Application or Patent No.: \_\_\_\_\_

Filed or Issued: \_\_\_\_\_

Title: A Method of Characterizing Spectrometer Instruments and Providing Calibration Models ....

I hereby state that I am

- ☐ the owner of the small business concern identified below:  
☒ an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF SMALL BUSINESS CONCERN Instrumentation Metrics, Inc.

ADDRESS OF SMALL BUSINESS CONCERN 2085 Technology Circle, Suite 302  
Tempe, AZ 85284

I hereby state that the above identified small business concern qualifies as a small business concern as defined in 13 CFR Part 121 for purposes of paying reduced fees to the United States Patent and Trademark Office. Questions related to size standards for a small business concern may be directed to: Small Business Administration, Size Standards Staff, 409 Third Street, SW, Washington, DC 20416.

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- ☒ the specification filed herewith with title as listed above.  
☐ the application identified above.  
☐ the patent identified above.

If the rights held by the above identified small business concern are not exclusive, each individual, concern, or organization having rights in the invention must file separate statements as to their status as small entities, and no rights to the invention are held by any person, other than the inventor, who would not qualify as an independent inventor under 37 CFR 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d), or a nonprofit organization under 37 CFR 1.9(e).

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☐ each such person, concern, or organization is listed below.

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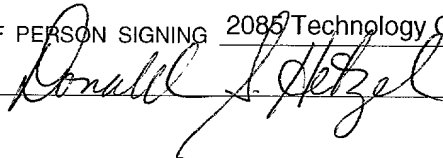
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NAME OF PERSON SIGNING Donald Hetzel

TITLE OF PERSON IF OTHER THAN OWNER President and CEO

ADDRESS OF PERSON SIGNING 2085 Technology Circle, Suite 302, Tempe, AZ 85284

SIGNATURE



DATE

7/17/00

**STATEMENT CLAIMING SMALL ENTITY STATUS  
(37 CFR 1.9(f) & 1.27(b))--INDEPENDENT INVENTOR**

Docket Number (Optional)  
IMET0040

Applicant, Patentee, or Identifier: Hazen et al.

Application or Patent No.: Unassigned

Filed or Issued: Herewith

Title: A Method of Characterizing Spectrometer Instruments and Providing Calibration Models ....

As a below named inventor, I hereby state that I qualify as an independent inventor as defined in 37 CFR 1.9(c) for purposes of paying reduced fees to the Patent and Trademark Office described in:

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☐ the application identified above.  
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Kevin H. Hazen  
NAME OF INVENTOR

Kevin H. Hazen  
Signature of inventor

7/26/00  
Date

Thomas B. Blank  
NAME OF INVENTOR

Thomas B. Blank  
Signature of inventor

7-26-00  
Date

Stephen L. Monfre  
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Stephen L. Monfre  
Signature of inventor

26 July 2000  
Date

STATEMENT CLAIMING SMALL ENTITY STATUS  
(37 CFR 1.9(f) & 1.27(b)) -- INDEPENDENT INVENTOR

Docket Number (Optional)  
IMET0040

Applicant, Patentee, or Identifier: Hazen et al.

Application or Patent No.: Unassigned

Filed or Issued: Herewith

Title: A Method of Characterizing Spectrometer Instruments and Providing Calibration Models ....

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- ☒ the specification filed herewith with title as listed above.  
☐ the application identified above.  
☐ the patent identified above.

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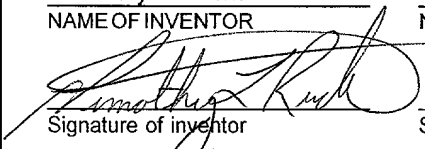
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Timothy L. Ruchti

NAME OF INVENTOR

NAME OF INVENTOR

NAME OF INVENTOR

  
Signature of inventor

Signature of inventor

Signature of inventor

7/26/2000  
Date

Date

Date

**A METHOD OF CHARACTERIZING SPECTROMETER  
INSTRUMENTS AND PROVIDING CALIBRATION MODELS  
TO COMPENSATE FOR INSTRUMENT VARIATION**

5

**CROSS-REFERENCE TO RELATED APPLICATION**

This application is a Continuation-in-part of U.S. Patent Application Ser. No.  
10 09/359,191; filed on July 22, 1999.

**BACKGROUND OF THE INVENTION**

**FIELD OF THE INVENTION**

15

The invention relates to variation in spectrometer instruments. More particularly  
the invention relates to characterizing spectrometer instruments by classifying  
their spectral responses into a limited number of clusters and developing  
calibration transfer models between clusters that compensate for instrument  
20 variations.

**DESCRIPTION OF THE PRIOR ART**

25

Many of the analytical applications for spectrometers require calibration data  
sets that are time-consuming and expensive to create. Typically, these  
calibrations are highly specific. For example, apparently identical instruments  
produced by the same manufacturer may exhibit minor instrument variations;  
such variations may be seen when one instrument is built with a component that  
varies slightly from the same component in another instrument. In addition, a  
30 calibration set for an instrument produced by one manufacturer is generally not  
suitable for a similar instrument produced by another manufacturer.  
Furthermore, repairs to a single instrument can cause the instrument's spectral

response to vary. As an instrument ages, it's spectral response may change. An instrument's spectral response may vary according to fluctuations in the operating environment. In applications requiring analysis of very low concentration analytes, non-invasive blood glucose prediction, for example, even minor instrument variation can introduce an unacceptable degree of error into the analysis. Providing another calibration model that takes the instrument's current spectral response into account can compensate for instrument variation. However, development of new calibration models is time-consuming, labor-intensive and costly.

In the development of spectroscopy-based analyzers for biomedical applications, there is a need for production of thousands to as many as millions of analyzers for a specific application. No methodology exists for providing calibrations for large numbers of instruments quickly and inexpensively.

Therefore, efforts have been directed at transferring calibrations from one analyzer to another. See, for example, E. Bouveresse, C. Hartmann, D. Massart, I. Last, K. Prebble, *Standardization of near-infrared spectrometric instruments*, Anal. Chem., vol. 68, pp. 982-990 (1996) and M. Defernez, R. Wilson, *Infrared spectroscopy: instrumental factors affecting the long-term validity of chemometric models*, Anal. Chem., vol. 69, pp. 1288-1294 (1997), and E. Bouveresse, D. Massart, P. Dardenne, *Calibration transfer across near-infrared spectrometric instruments using Shenk's algorithm: effects of different standardization samples*, Analytica Chimica Acta, vol. 297, pp. 405-416, (1994) and Y. Wang, D. Veltkamp, B. Kowalski, *Multivariate instrument calibration*, Anal. Chem., vol. 63, pp. 2750-2756 (1991).

Most of the reported methods of calibration transfer have been applied in situations involving high-concentration analytes, wherein the signal-to-noise ratio is high. Because these currently known methods act as a smoothing function when transferring calibrations, they degrade the signal to noise that

can be observed, thus hindering analysis of low concentration analytes. Additional problems of changes in resolution or bandwidth across time or between instruments have not been addressed.

5 Furthermore, the currently known methods have only been successfully applied in situations involving a small number of instruments. The reported methods are not capable of modeling the complexity encountered when large numbers of instruments are involved.

10 A need exists for the calibration of large numbers of analyzers. It would be desirable to provide a means of reducing the complexity inherent in the transfer of calibrations to large numbers of analyzers. It would also be advantageous to provide a means of transferring calibrations without significant degradation of the signal-to-noise ratio, rendering calibration transfer practical in analysis of  
15 low concentration analytes.

### **SUMMARY OF THE INVENTION**

20 The invention provides a method of characterizing large numbers of spectrometer instruments by classifying their spectra into a limited number of previously defined clusters according to similarity of spectral features and performance characteristics. The method may also be used to track variation over time within a single instrument. The spectral features used for classification  
25 may be related to known instrument parameters, or they may be abstract features derived using a variety of computational methods. The clusters are defined in advance based on an exemplar data set, using either supervised or unsupervised methods. Calibration models for each cluster compensate for instrument variation, either across instruments or across time within a single  
30 instrument.



In a preferred embodiment of the invention, calibration models are provided using a method of calibration transfer wherein the clusters are mapped to each other, so that a calibration transferred from one cluster to another need only model the difference between the two clusters. In an alternate embodiment, a different calibration is separately calculated for each cluster. In either embodiment, the number of calibration transfers is significantly reduced since each cluster represents a multitude of instruments.

## **BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1 provides a block schematic diagram of a method of characterizing spectrometer instruments by clustering according to spectral features, according to the invention;

Figure 2 provides a flow diagram of a method of generating calibration models by transferring a master calibration to slave calibration models, according to the invention;

Figures 3A and 3B illustrate decreases in spectral cutoff related to decreases in detector temperature in a spectrometer instrument; and

Figure 4 illustrates changes in light throughput related to changes in source temperature in a spectrometer instrument.

## **DETAILED DESCRIPTION**

The invention provides a method of characterizing spectrometer instruments by classifying spectral responses from a large number of spectrometers (analyzers) into a limited number of previously defined clusters. The clusters constitute groups that are defined based on the similarity of specific features.

Grouping of instruments according to spectral features and performance characteristics reduces the spectral variation between instruments in a given group. Therefore, spectral measurements corresponding to an individual cluster are more homogeneous than those from the entire group of analyzers.

5 Calibrations created for each cluster may then be utilized for subsequent analysis. The calibration created for a cluster will have instrument variations included in the model that mirror variations resulting from the particular analyzer employed for the subsequent analysis. Calibration models specific to the clusters are expected to be less complex and have an improved level of  
10 accuracy. Therefore, multivariate analysis will require fewer factors to model instrument variation resulting in earlier factors modeling the sample and earlier factors modeling small absorbing analytes. The net result is that fewer factors are required for sample analysis and a more robust algorithm is created.

15 In one embodiment of the invention, a separate calibration data set is required for every cluster, requiring a large number of samples in a calibration set for every cluster. In the preferred embodiment, sufficient samples for a calibration model are only required in a single cluster. Principal features defining that cluster and other clusters are determined, and the clusters are mapped to each  
20 other, revealing the specific differences from one cluster to another. Subsequently, the calibration from the initial cluster is transferred to another cluster based upon the specific differences between clusters.

The parent application to the current application, S. Malin and T. Ruchti, *An*  
25 *intelligent system for noninvasive blood analyte prediction*, U.S. Patent Application Ser. No. 09/359,191 (July 22, 1999), provides a detailed description of a method of classifying spectral measurements into previously defined clusters through similarities observed in absorbance spectra. The classification system of the sampled tissue volume of the subjects is herein expanded to  
30 include classification of instrumentation variations.

Referring now to Figure 1, a general method of classifying spectral measurements into previously defined clusters is represented. Briefly the steps of the method are:

- 5        1. Measurement. (11)
2. Classification (12), in which the measured spectrum is assigned membership in any one of a number of predefined clusters 13.
- 10      3. Calibration (14), in which calibration models suited to each cluster are provided.
4. Identifying outliers (15)

#### MEASUREMENT

- 15    In general, instrumental variations may affect spectral response by producing either signal intensity changes, bandwidth changes, wavelength changes, or combinations thereof. These instrumental variations may include:

1. wavelength shifts;
2. nonlinear wavelength shifts;
- 20    3. wavelength expansions;
4. wavelength contractions;
5. nonlinear wavelength expansions;
6. source intensity drifts;
7. blackbody profile changes;
- 25    8. bandwidth changes;
9. resolution changes;
10. baseline deviations;
11. change with time;
12. temperature effects;
- 30    13. detector response;

14. differences in optical components (e.g. long-pass filters or fiber optics);
15. variation related to mounting of references;
16. differences in the optical interface to the sample (fiber spacing);
17. linearity;
- 5 18. detector cut-off;

and many others, which will be apparent to those skilled in the art. Spectra used for classification will typically be those of commonly known standards. Standards particularly useful for classifying shifts observed in the wavelength axis include polystyrene, rare earth oxides: holmium oxide, erbium oxide or  
10 dysprosium oxide, for example; or combinations thereof. Standards such as the diffuse reflectance standards supplied by Labsphere, Inc. (North Sutton NH) may be used to classify shifts in the intensity axis. Spectra of samples may also be used for classification. Additional intensity and wavelength standards will be known to those skilled in the art.

15 In the specific case of near-IR noninvasive glucose determination these standards cover the near-IR spectral region. Additional spectroscopy and chromatography-spectroscopy hyphenated techniques such as AA (atomic absorption spectroscopy) or GC-MS (gas chromatography mass spectroscopy)  
20 will each require their own standards which are known by those skilled in the art. Additionally, spectra of tissue phantoms collected on an instrument may also be used to characterize that instrument. Tissue phantoms are helpful in characterizing an instrument because spectra of these phantoms simulate noninvasive spectra of living tissue. There are tissue phantoms that simulate the  
25 absorption coefficients of various skin tissues; while others simulate the scattering coefficients of the body. Some common simulants include:

1. milk and milk products
2. milk products in combination with India ink, used to adjust the absorption coefficient;

3. emulsions of fatty substances in water maintained in solution with an emulsifier such as lecithin. One such commercial product is INTRALIPID, supplied by Kabivitrum AB (Stockholm, Sweden);
4. Intra-serum and Intra-gel. See K. Hazen, J. Welch, S. Malin, T. Ruchti, A Lorenz, T. Troy, S. Thenadil, T. Blank, *Intra-serum and intra-gel for modeling human skin tissue*, U.S. Patent Application Ser. No. 09/502,877 (February 10, 2000).

Other scattering and absorbing mediums are known to those skilled in the art.

Concentrations of these tissue simulants may be adjusted to match the scattering and absorption coefficients of body tissues such as skin or internal organs.

It will also be apparent that a set of exemplar measurements is required for cluster definition and development of calibration models, in addition to the actual spectral measurements utilized for classification.

#### CLASSIFICATION

New spectral measurements are passed to a pattern classification system that classifies the measurements into previously defined clusters having a high degree of internal consistency through spectral features related to instrumental variation.

The classification itself includes the following steps:

1. Feature extraction; and
2. Classification of features according to a classification model.

#### FEATURE EXTRACTION

The process of feature extraction is more fully described in the parent application to the current application, U.S. Patent Application Ser. No. 09/359,191, *supra*. Feature extraction is any mathematical transformation that

enhances a particular aspect or quality of the data that is useful for interpretation. Features may be of two categories:

1. Abstract, and
2. Simple.

Instruments may be classified by abstract features, meaning that they may be classified using computational methods. These methods may be supervised or unsupervised. Examples include plotting primary principal components versus one another and identifying clusters of results; discriminant analysis, such as measurement of the Mahalanobis distance, and k-means clustering. Additional methods will be readily apparent to those skilled in the art.

It is important to note that the clustering techniques listed above are not mutually exclusive. Clustering of raw spectra into one or more groups may be achieved through one or more of these methods and with combinations of these approaches.

Simple features are derived from an *a priori* understanding of the system, and can be related directly to an instrument parameter or component (or parameters or components). For example, the measured bandwidth, noise characteristics, or linearity and detector cutoffs.

#### CLUSTER DEFINITION

As indicated above, clusters must have been previously defined, using a data set of exemplar spectral measurements. Cluster definition is the assignment of the measurements in the exploratory data set to clusters. After cluster definition, the measurements and class assignments are used to determine the mapping from the features to cluster assignment.

Cluster definition is performed using either supervised or unsupervised methods. In the supervised case, clusters may be defined using specific knowledge of the system. For example, source intensity and detector temperatures have specific effects on the spectra, as demonstrated further below. The use of *a priori* information in this manner is the first step in supervised pattern recognition, which develops classification models when the class assignment is known.

Alternatively, clusters may be defined in an unsupervised manner using abstract features such as clustering within plots of principal component scores 'x' versus spectral loading 'y'. The result is that within a given cluster, all of the spectra have the same characteristics (interferences, instrument variations or sample issues). Clusters formed from features with physical meaning can be interpreted based on the known underlying phenomenon causing variation in the feature space.

## CLASSIFICATION

Subsequent to class definition, a classifier is designed through supervised pattern recognition. A model is created, based on cluster definitions, that transforms a measured set of features to an estimated classification. The classification model is a method for determining a set of similarity measures with the predefined clusters. A decision rule assigns membership on the basis of a set of measures calculated by a decision engine.

## CALIBRATION

Once the spectra have been classified into clusters, calibration models are required for each cluster. Provision of the clusters is by one of two methods. In the preferred embodiment, a master calibration is developed for a first cluster, subsequently the master calibration is transferred to slave calibrations, one for each remaining cluster. An alternate embodiment, described further below, individually calculates calibrations for each cluster.

In the case of spectra collected utilizing a master and slave instrument, the term “calibration transfer,” as commonly used in the art, may have different meanings. Calibration transfer may refer to transforming the slave spectral to look like the master spectra or *vice versa*. Additionally, spectra from both the master and the slave can be transferred to a common standard spectrum not present in the master or slave data sets. Furthermore, calibration transfer can refer to preprocessing steps, multivariate adjustments of the sample spectra, or adjustments to the predicted analyte concentrations based upon standards.

Referring now to Figure 2, the process of calibration transfer is shown. Calibrations 14 are required for each of  $n$  clusters. A master calibration 21 is calculated for a first cluster; then, to provide calibrations for each of the remaining  $n$  clusters, the master calibration is transferred to slave calibrations.

In this case, Calibration transfer refers to the process of transforming spectra on a slave instrument to match the characteristics of the master such that the master calibration can be applied to the slave spectra. For clusters, calibration transfer refers to the process of transforming spectra on a slave instrument to match the characteristics of the master such that a new calibration is generated that satisfies the specification of a cluster other than the one for which the master cluster was developed. The clusters may also be organized into groups of clusters, so that the master calibration is transferred to slave calibrations 23, which in turn are transferred to the slave calibration for the various clusters within each group.

Prior art methods of calibration transfer have been unsuccessful at modeling the complexity involved in providing calibration models for large numbers of instruments. Classifying the spectral measurements in to clusters having a high degree of internal consistency reduces the complexity of the problem to a level that makes it possible to apply calibration transfer to large numbers of instruments. Clustering the acquired spectra into a limited number of subgroups



allows the calibration transfer issues to be broken up into subsets so that only a subset of the overall issues needs to be addressed between any two clusters. The result is that within a given cluster, all of the spectra have the same characteristics. A calibration is generated for a given cluster using spectra of samples containing the limited number of characteristics of that cluster. This eliminates having to deal with all of the variations possible in the raw measurements, significantly reducing the complexity that needs to be modeled by the calibration. Thus, the calibration utilized for a given cluster will have instrument variations included in the model that are similar to variations resulting from the analyzer employed. As each cluster has its own specification, the calibration transfer technique need only deal with the differences between those two clusters. For example, if the only difference between the clusters is a linear x-axis shift, then the calibration transfer technique need only deal with that parameter. This allows a more specific calibration transfer technique to be employed that is more robust, resulting in fewer factors, since fewer instrument variations need to be modeled. This will result in analysis of lower concentration analytes due to retention of signal to noise in the calibration transfer step.

Typically, calibration transfer techniques have to address instrument-to-instrument variations, such as wavelength shifts, nonlinear wavelength shifts, wavelength expansions (contraction), nonlinear wavelength expansions, source intensity drifts, blackbody profile changes, bandwidth (resolution) changes, baseline deviations, change with time, temperature effects and others known to those skilled in the art.

However, in addition to instrumentation issues in calibration transfer, sample composition and sample handling considerations are very important in calibration transfer. Therefore, every sample analyzed for prediction of results should be an interpolation within the matrix space of the calibration data set; otherwise the calibration may not calculate an accurate prediction of analyte

concentration. For example, if the calibration data set contains glucose samples ranging from 40 to 400 mg/dL, then predictions on samples with glucose outside of this range are suspect.

5 Thus, an important additional benefit of the invented classification algorithm is that outlier spectra may be identified, as shown in Figure 1. Each cluster has its own set of classification requirements. If a spectrum does not fall within the parameters of a given cluster, another cluster must be found which has parameters allowing analysis of that spectrum. If no cluster is found, then the  
10 sample is reported as an outlier rather than having a value reported for the analyte that may not be correct. In this manner, analysis on samples or instruments for which no satisfactory calibration model has been developed is prevented.

15 Spectra classified as outliers may assume two forms. In some instances, the outlier spectrum is close to a given cluster. In such a case, conventional calibration transfer techniques may be applied to this spectrum to transform the spectrum such that it falls within one of the clusters for which calibrations exist. In case of failure, the spectrum remains classified as an outlier, as will spectra  
20 that are characterized as gross outliers.

Classification and calibration transfer need not be limited to differences in instrumentation; it may also be applied to sample spectra for analyte prediction. For example, a cluster may be defined for healthy 18 to 30 year old men. A  
25 noninvasive glucose model may be built for this narrow demographic. A separate cluster may be for 18 to 30 year old non-pregnant women. Differences between the two clusters such as body fat and sampled volume may be addressed and a calibration transfer technique may be optimized for those differences based on relatively few spectra, thus allowing a glucose model  
30 initially generated for a narrow demographic to be gradually expanded.

The foregoing embodiment does not require calibrations to be built for every cluster, and thereby provides the important advantage of sparing the considerable time, money and effort required for building a separate calibration for every cluster. The actual calibration transfer technique employed may be selected from the many algorithms known to those skilled in the art.

An alternative embodiment classifies spectra into clusters, as in the preferred embodiment, and builds individual calibrations for each cluster. The requirement for calibration transfer is eliminated at the expense of the requirement for more spectra. However, an additional measure of reliability is gained by having clusters with well-defined and narrow parameters. As in the previous embodiment, fewer instrument variations need to be modeled so that early factors can focus on analyte information, resulting in a more robust model.

While the foregoing description of the invention has been directed to characterizing different instruments, the invented method also finds application in classifying spectra from a single instrument according to known variations in instrument components or known environmental variations. Two examples are described.

1. The cutoff of the 2.6  $\mu$ m InGaAs detector employed in many near-IR analyzers blue shifts as the temperature of the detector decreases. Air spectra collected on a NICOLET 860, supplied by the Nicolet Instrument Corporation (Madison WI) with the InGaAs detector ranging from 0 to  $-20^{\circ}\text{C}$  are presented in Figure 3A. The spectral cutoff region from 2400 to 2600 nm is expanded in Figure 3B. The cut-off decreases as the detector temperature decreases. Using reference or air spectra, a simple analysis, such as determining the wavelength at which 10% of the peak intensity is observed, allows the instrument to be classified as to whether the detector is properly cooled and to the extent that it was cooled.

2. As a tungsten halogen source increases in temperature, the blackbody emission increases in magnitude and additional light throughput is observed. For example, in diffuse reflectance spectra of a 5% Labsphere diffuse reflectance standard, the overall intensity is observed to increase as the source temperature increases, as shown in Figure 4. This effect can be used to classify the instrument in terms of the source temperature and total light throughput.

It is a relatively simple task to characterize the instrument in terms of additional components. Examples are slit width, affecting bandwidth or room temperature, affecting total light throughput. There are, however, a limited number of components to a spectrometer; it has been observed that instruments group into a relatively small number of clusters.

Once an instrument, or a given spectrum, is classified into a cluster, the appropriate calibration routine can be employed. A single analyzer may be loaded with multiple calibration routines, as the instrument may vary during its lifetime. In fact, environmental factors may cause the appropriate calibration to change with every spectrum collected.

This instrument classification approach was designed for use on noninvasive glucose analyzers where glucose is measured using diffuse reflectance spectra of skin on the human body. However, the same technology can be applied to any form of noninvasive analysis including but not limited to: noninvasive analysis of albumin, globulin, urea, creatinine, oxygen, hemoglobin A<sub>1</sub>C and electrolytes such as Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup>. The technology may also be utilized in biomedical applications.

The classification approach disclosed here finds application in various fields of endeavor, the agricultural field, for example. Exemplary agricultural

applications are: analysis of fat in milk, protein or moisture analysis in wheat, or analysis of sugars in fruits. The classification approach may also benefit pharmaceutical companies in the analysis of intact tablets or in the characterization of raw materials. Finally, petrochemical companies may utilize the method in classification of fuels, fuel by-products and in raw fuel materials. In general, this technique is useful wherever a large number of analyzers are utilized to quantify analytes in samples.

Although the invention is described herein with reference to the preferred embodiment, one skilled in the art will readily appreciate that other applications may be substituted for those set forth herein without departing from the spirit and scope of the present invention. Accordingly, the invention should only be limited by the claims included below.

## **CLAIMS**

What is claimed is:

5

1. A method of characterizing spectrometer instruments according to instrumental variation, comprising the steps of:

providing standard spectral measurements from at least one spectrometer instrument; and

10

classifying said spectral measurements into predefined clusters on the basis of extracted spectral features; and

providing calibration models for each of said predefined clusters, wherein said calibration model compensates for said instrumental variation.

15

2. The method of Claim 1 wherein said instrumental variation comprises any of:

wavelength shifts;

nonlinear wavelength shifts;

wavelength expansions;

20

wavelength contractions;

nonlinear wavelength expansions;

source intensity drifts;

blackbody profile changes;

bandwidth changes;

25

resolution changes;

baseline deviations;

changes over time;

temperature effects;

detector response;

30

differences in optical components (e.g. long-pass filters or fiber optics);

variation related to mounting of references;

differences in the optical interface to the sample (fiber spacing);  
linearity; and  
detector cut-off.

5     3.     The method of Claim 1, wherein said standard spectra are measured on  
a plurality of spectrometer instruments.

4.     The method of Claim 1, wherein said standard spectral are measured on  
a single spectrometer instruments at successive time intervals.

10

5.     The method of Claim 1, wherein said classifying step comprises the steps  
of:

extracting features; and  
classifying said features according to a classification model and decision

15

rule.

6.     The method of Claim 5, wherein said feature extraction step comprises  
any mathematical transformation that enhances a particular aspect or quality of  
data that is useful for interpretation.

20

7.     The method of Claim 3, wherein said classification model comprises  
means for determining a set of similarity measures with predefined classes.

25

8.     The method of Claim 5, wherein said decision rule comprises means for  
assigning class membership on the basis of a set of measures calculated by a  
decision engine.

9.     The method of Claim 4, wherein individual features are divided into two  
categories, said categories comprising:

30

abstract wherein said features are extracted using various computational  
methods ; and

simple features that are derived from an *a priori* understanding of a system, wherein said feature is directly related to an instrument parameter or component.

5 10. The method of Claim 7, wherein said abstract features are calculated using any of:

plotting primary principal components versus one another and identifying resulting clusters;

discriminant analysis; and

10 k-means clustering.

11. The method of Claim 5, wherein said classification step further comprises the step of employing factor-based methods to build a model capable of representing variation in a measured spectrum related to variations in spectral response;

15 wherein projection of a measured absorbance spectrum onto said model constitutes a feature that represents spectral variation related to instrument variation.

20 12. The method of Claim 5, wherein said classifying step further comprises the steps of:

measuring the similarity of a feature to predefined clusters; and

assigning membership in a cluster.

25 13. The method of Claim 5, further comprising the step of:  
assigning measurements in an exploratory data set to clusters.

14. The method of Claim 13, further comprising the step of:  
using measurements and class assignments to determine a mapping  
30 from features to cluster assignments.



15. The method of Claim 13, further comprising the steps of:

defining clusters from said features in a supervised manner, wherein each set of features is divided into two or more regions, and wherein classes are defined by combinations of feature divisions;

5 designing a classifier subsequent to class definition through supervised pattern recognition by determining an optimal mapping or transformation from the feature space to a class estimate which minimizes the number of misclassifications; and

10 creating a model based on class definitions which transforms a measured set of features to an estimated classification.

16. The method of Claim 1, further comprising the step of providing calibration models for analysis of new sample measurements.

15 17. The method of Claim 16, wherein said calibration models model differences between said predefined clusters.

20 18. The method of Claim 16, wherein a master calibration model is developed for a first of said clusters from a set of exemplar spectra with reference values and pre-assigned classification definitions.

25 19. The method of Claim 18, further comprising the step of transferring said master calibration model to a plurality of slave calibration models, wherein a slave calibration model is calculated for each remaining cluster, and wherein a transform modifies said master calibration model to a slave calibration model in accordance with principal features defining each of said classes.

30 20. The method of Claim 19, wherein said transferring step comprises the steps of:

transferring said master calibration model to a first slave calibration model;

transferring said first slave calibration model to a second slave calibration model;

5 and repeating said transfer from one slave calibration model to another slave calibration model, until a calibration has been provided for each of said predefined clusters;

wherein a transform modifies said transferred calibration models in accordance with principal features defining each of said clusters.

10

21. The method of Claim 18, further comprising the step of transferring said master calibration model to a plurality of slave calibration models, wherein a slave calibration model is calculated for each remaining cluster, and wherein a transform modifies said slave calibration model to said master calibration model in accordance with principal features defining each of said classes.

15

22. The method of Claim 21, wherein said transferring step comprises the steps of:

transferring said master calibration model to a first slave calibration model;

20

transferring said first slave calibration model to a second slave calibration model;

and repeating said transfer from one slave calibration model to another slave calibration model, until a calibration has been provided for each of said predefined clusters;

25

wherein a transform modifies said transferred calibration models in accordance with principal features defining each of said clusters.

23. The method of Claim 16, wherein a different calibration model is developed for each class, and wherein said calibration models are developed

30

from a set of exemplar spectra, with reference values and pre-assigned cluster definitions.

24. The method of Claim 23, wherein a spectrum is assigned to one of many predefined clusters for which a calibration model has been developed.

25. The method of Claim 1, further comprising the steps of:  
providing new spectral measurements;  
comparing said new spectral measurements to each of said pre-defined clusters according to extracted spectral features;  
reporting those measurements as outliers for which a matching cluster is not found.

26. A method of developing calibration models for spectral analysis comprising the steps of:  
defining clusters from an exemplar data set of spectral measurements, wherein said clusters exhibit a high degree of internal similarity;  
mapping said clusters to one another, wherein principal features distinguishing clusters from one another are determined;  
calculating a calibration model for a first of said clusters, said calibration model comprising a master calibration;  
transferring said master calibration to at least one slave calibration, wherein a slave calibration comprises a calibration derived by applying a transform to slave spectra such that the master calibration now models the difference between the master cluster and another cluster corresponding to said slave spectra.

**ABSTRACT**

Spectrometer instruments are characterized by classifying their spectra into  
5 previously defined clusters. The spectra are mapped to the clusters and a  
classification is made based on similarity of extracted spectral features to one of  
the previously defined clusters. Calibration models for each cluster are provided  
to compensate for instrumental variation. Calibration models are provided either  
10 by transferring a master calibration to slave calibrations or by calculating a  
separate calibration for each cluster.

A simplified method of calibration transfer maps clusters to each other, so that a  
calibration transferred between clusters models only the difference between the  
15 two clusters, substantially reducing the complexity of the model.

```

graph TD
    Measurement[Measurement 11] --> Classification[Classification 12]
    Classification --> Cluster1[Cluster 1]
    Classification --> Cluster2[Cluster 2]
    Classification --> Cluster3[Cluster 3]
    Classification --> Dots1[...]
    Classification --> Clustern[Cluster n]
    Cluster1 --> Calibration1[Calibration 1]
    Cluster2 --> Calibration2[Calibration 2]
    Cluster3 --> Calibration3[Calibration 3]
    Dots1 --> Dots2[...]
    Clustern --> Calibrationn[Calibration n]
    Calibration1 --> Outlier[outlier 15]
    Calibration2 --> Outlier
    Calibration3 --> Outlier
    Dots2 --> Outlier
    Calibrationn --> Outlier
  
```

Figure 1 14

008460-E2649960

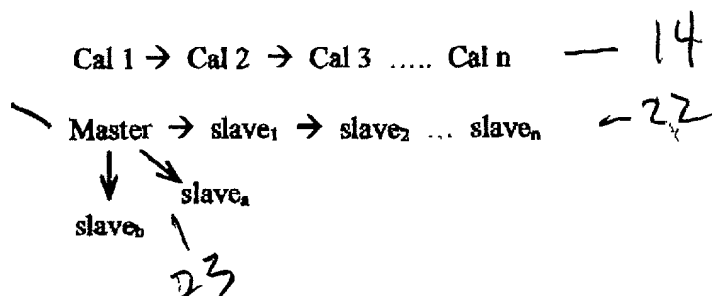


Figure 2

## Varying detector temperatures

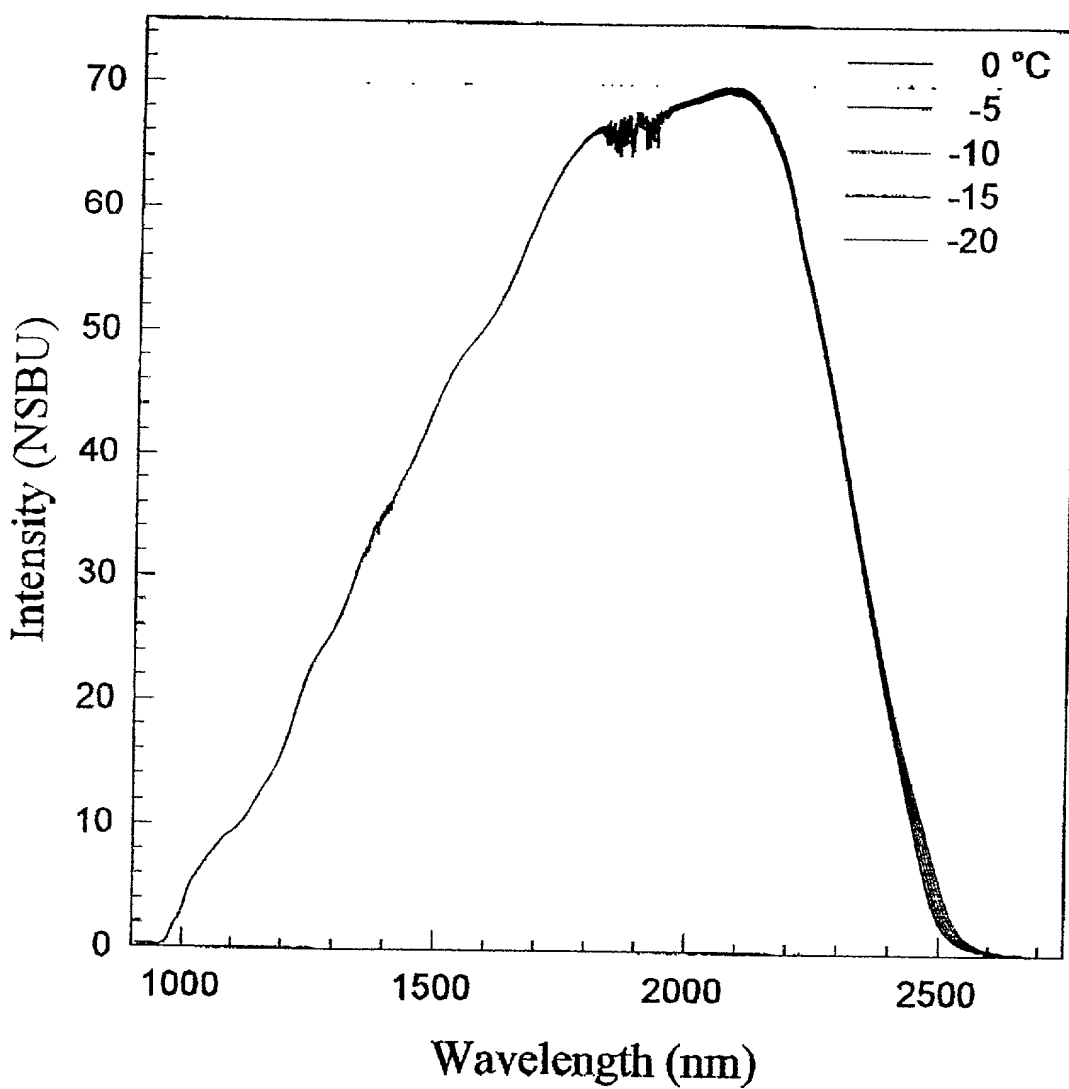


Figure 3A.

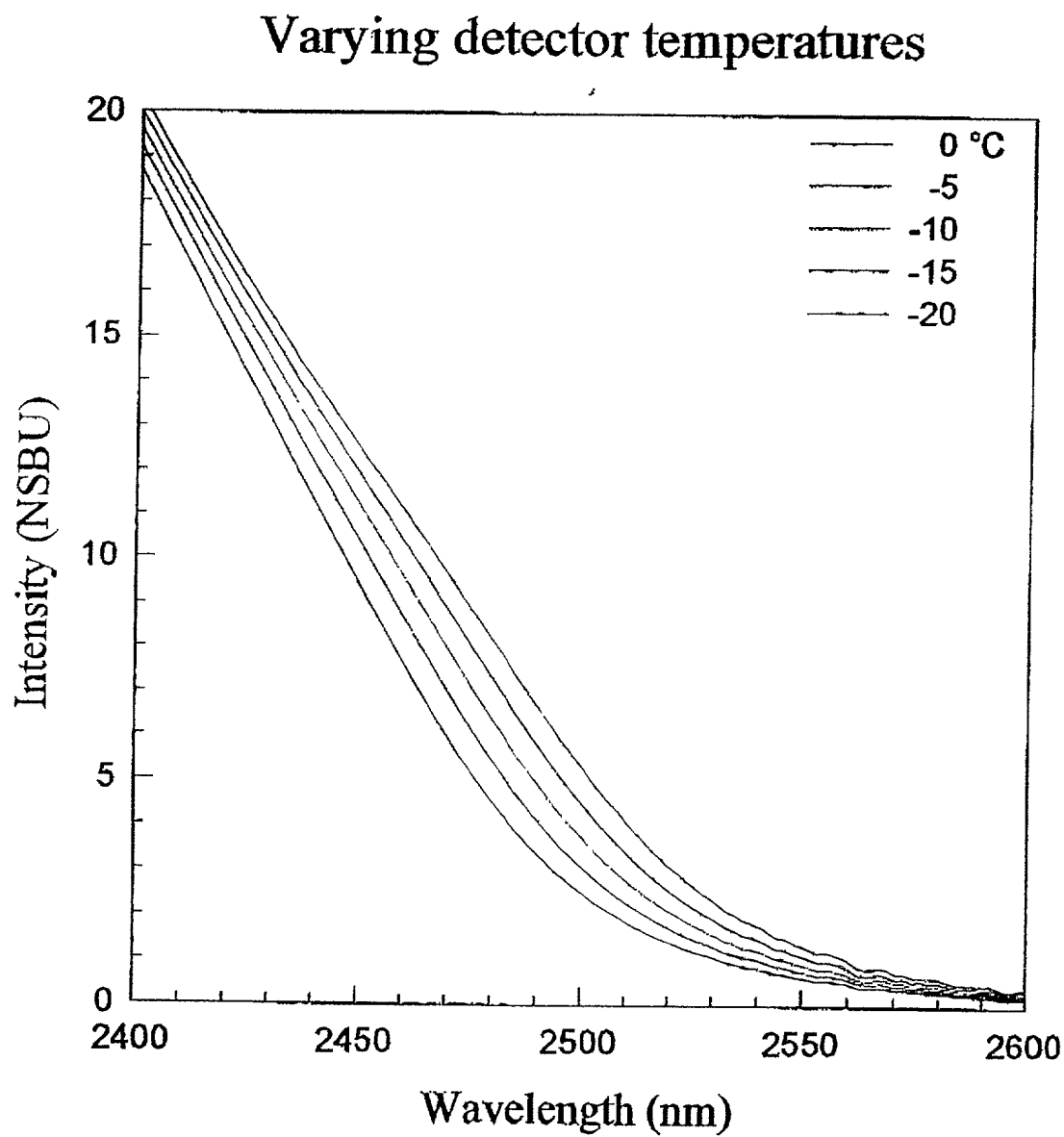


Figure 3B



## Variation of Intensity with Source Temperature

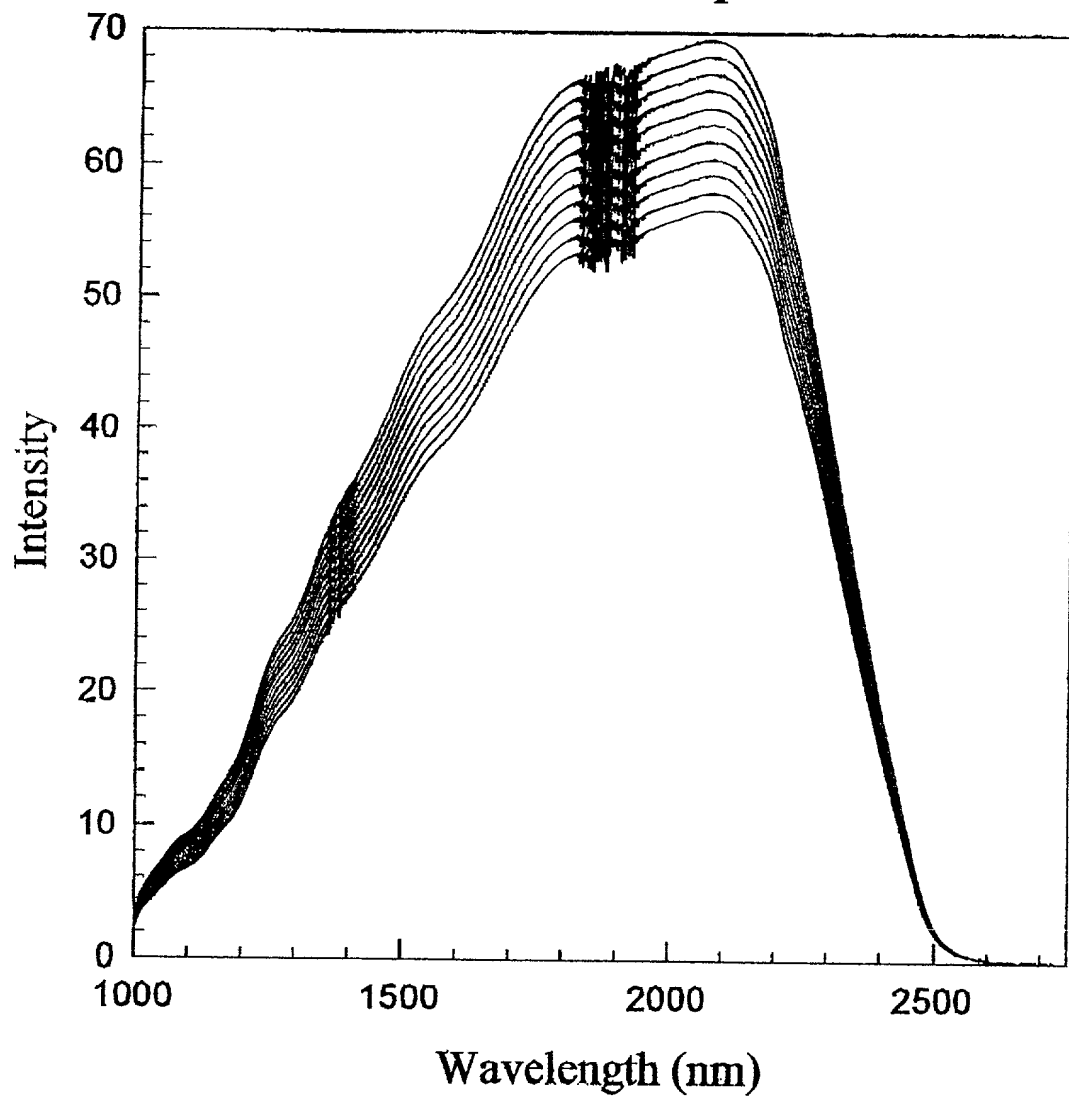


Figure 4

DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name;

I believe I am the original, first, and sole inventor (if only one name is listed below) or an original, first, and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**A METHOD OF CHARACTERIZING SPECTROMETER INSTRUMENTS AND PROVIDING CALIBRATION MODELS TO COMPENSATE FOR INSTRUMENT VARIATION**

the specification of which (check one) X is attached hereto, or \_\_\_\_ was filed on \_\_\_\_\_ as Application Serial No. \_\_\_\_\_ and was amended on \_\_\_\_\_ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56(a).

=====

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
			Yes	No
Number	Country	Day/Month/Year Filed	_____	_____
Number	Country	Day/Month/Year Filed	_____	_____

=====

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

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=====

I hereby claim the benefit under Title 35, United States code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

09/359,191                      JULY 22, 1999                      Pending - Utility  
Application Ser. No.                      Filing Date                      Status: Patented, Pending, Abandoned

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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